REMARKS

Claims 37-41, 46, and 49-62 are pending in the instant application. Claims 46 and 49 have been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Withdrawn Objections/Rejections

Applicants acknowledge the withdrawal of the objection to claims 39 and 61-62; the rejection of claim 42 under 35 U.S.C. 112, second paragraph; the rejection of claim 50 under 35 U.S.C. 112, first paragraph; and the rejection of claims 37-40, 42-43, 47-48, 50-62 under 35 U.S.C. 102(b) as being anticipated by James et al. (US 6228401).

II. Rejection of the Claims Under 35 U.S.C. §112

Claims 46 and 49 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner suggests that in so far as claim 46 currently depends from canceled claim 45 and claim 49 currently depends from canceled claim 48, the metes and bounds of claims 46 and 49 are unclear.

In an earnest effort to facilitate the prosecution of this application, Applicants have amended claims 46 and 49 to refer to base claim 37. In light of this amendment, Applicants respectfully request that this rejection be withdrawn.

III. Rejection of the Claims Under 35 U.S.C. §103

While the Office Action states that "Claims 37-40, 46, and 49-6237-40, 42-43, 47-48, 50-62" have been rejected under 35 U.S.C. 103(a) as being unpatentable over James et al. (U.S. 6,228,401) Applicants will assume for the sake of expediting the prosecution of this application that the intent was to reject claims 37-40, 46, and 49-62. The Examiner contends that James et al. teach the exact same ingredients as required by the instant claims as well as the use of rotary cutters which is a type of forced-action mixer, which is the same process recited in the instant product-by-process claims. The Examiner acknowledges that James et al. fail to explicitly teach wherein the size of 50% of the flutamide particles in the pharmaceutical formulation is greater than 26 microns as required in independent claim 37, or wherein 90% of the flutamide particles is greater than 130 microns as required by claim 46, or that the specific surface area less than 0.35 m2/cm3 as required by claim 49. However, the Examiner asserts at pages 7 and 8:

> James et al. with respect to particle size and surface area teaches the following. James teaches specific examples wherein the X_{50} value of the flutamide particles is greater than 20 µm (example 5, column 7, see example 3 from the table at lines 45-47, X_{50} =20.99 µm), and an example wherein the flutamide particles have a specific surface area of 0.47 m^2/cm^3 (example 5, column 7, see example 3 from the table at lines 45-47). James more generally teaches that the X_{50} for the particles is less than 26.0 µ (col. 2, lines 23-24) and that typical X_{90} values for the particles is from about 10 to about 130.0 µ (col. 2, lines 28-29). With respect to claim 49 which specifies that the flutamide particles have specific surface area of 0.35 m^2/cm^3, James teaches flutamide particles having a specific surface area of at least about 0.35 $^{m2}/cm^3$. About 0.35 m^2/cm^3 overlaps with and thereby makes obvious the

> claimed value of less than 0.35 m^2/cm^3. James et al. teach that means of achieving these particle sizes, distributions and surface areas include milling, but also the use of rotary cutters (i.e. forced-action mixer, see discussion above regarding page 10 of the instant specification), see col. 2, lines 37-38. Also, James teaches that particles of flutamide are known that range from 5 to 240 microns in size (col. 1, line 47). It is also well known in the art that that varying the mixing speed, the amount of flutamide fed into the mixer and the mixing period all influence the resulting size and surface area of the resultant flutamide particles. James also teaches that flutamide is relatively insoluble (col. 1, line 38) and that flutamide has a consistency which is difficult to mill due to the fact that it readily agglomerates and give inconsistent results (col. 2, lines 46-48). James teaches that the specific surface area of flutamide is critical for determining bioavailability of flutamide (col. 1, lines 52-54). James also teaches that the range of particle sizes contained in a sample of flutamide influences the bioavailability and thus the therapeutic benefit of the drug (col. 2, lines 17-20).

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to arrive at particles with an X_{50} value greater than 26 microns and X_{90} values greater than 60 microns or 130 microns and particles with a specific surface area of less than 0.35 m^2/cm^3 based on the teachings of James at the time of the instant invention with a reasonable expectation of success and one would have been motivated to do so to affect the resultant particle size.

Claim 41 has also been rejected under 35 U.S.C. 103(a) as being unpatentable over James et al. in further view of Neri et al. (US 3,995,060). It is suggested that while James et al. fail to teach that flutamide has been subjected to recrystallization

as necessitated by claim 41, Neri et al. compensate for this deficiency in the teachings of the primary reference.

Applicants respectfully traverse these rejections.

At the outset, Applicants respectfully assert that the Examiner's conclusions are inconsistent. On the one hand, the Examiner acknowledges that pending claims 37, 46 and 49 are novel because James et al. do not teach a X_{50} value of flutamide particles greater than 26 µm, or a X_{90} value greater than 130 µm, or a specific surface area less than 0.35 m^2/cm^3. See pages 3 and 7 of the Office Action. Nevertheless, at page 13 of the Office Action, the Examiner concludes that "James teaches X_{50} and X_{90} values that overlap with those values claimed." This conclusion, however, is not supported by the evidence on which the action relies and is also in complete contrast to the statements on pages 7 and page 8 of the action. Nowhere do James et al. teach or suggest a flutamide particle size with X_{50} of greater than 26 µm that would provide desired/necessary bioavailability. For instance, the largest exemplified X_{50} value of James et al. is 20.99 µm, which is more than 20% smaller than the claimed 26 µm.

The influence of the particle size on the bioavailability is addressed at col. 2, lines 17-25 of James et al., wherein it is stated:

> "It has further been discovered that the range of particle sizes contained in any sample can also influence the bioavailability. As such, another aspect of the present invention is flutamide … in which fifty percent (50%) of the particles of each sample (X_{50}) is less than 26.0 µ, preferably in the range from about 5.0 µ to about 20.0 µ." (emphasis added)

Concerning surface area, column 1, lines 52-59 of James et al. further states:

> "It has been discovered that the specific surface area of flutamide used in formulating final dosage forms is critical, and that the particle size range stated in the '060 patent [Neri et al.] will not provide adequate bioavailability of flutamide. In fact, it has been discovered that the particle size and specific surface area/volume (m^2/cm^3) of flutamide must meet specific criteria to ensure adequate bioavailability of formulated flutamide."
> (emphasis and bracketed expression added)

From the foregoing it follows that a skilled artisan would have had no reason to conclude that the instantly claimed flutamide particles possess adequate bioavailability. Therefore, the Examiner's assertion of motivation to modify the teachings of the cited references to arrive at the claimed particle size is not well-founded.

With respect to the use of unmilled flutamide particles, page 9 of the Office Action relies upon James et al. (column 2, paragraph spanning lines 30-45). There is, however, no basis in the cited passages of James et al. to support the argument for using unmilled flutamide. Indeed, this section of James et al. states:

> "Flutamide … having the specific surface area and/or the X_{50} and/or X_{90} values as set forth here in above, is prepared through milling techniques generally well known to one of ordinary skilled in the art, without causing chemical and/or heat degradation of flutamide API." (emphasis added)

This is in complete contradiction to the Examiner's assertion that one of skill in the art would be motivated to use less milling based upon the teachings of James et al. because excess milling/mixing can lead to heat degradation of the product.

Clearly, James et al. teaches that the skilled person can use standard techniques to mill flutamide without any problems.

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

In the instant case, the whole of the teachings of James et al. instructs the skilled artisan that particle size is critical and, more importantly, teaches that you should never go above an X_{50} of 26.0 µm; with preference for particles in the range of 5.0 µm to 20.0 µm (see column 2, lines 23-25). Thus, James et al. unquestionably teaches away from the claimed invention.

In so far as Neri et al. fails to compensate for the deficiencies in the teachings of the primary reference, it is therefore respectfully requested that these rejections under 35 U.S.C. 103(a) be reconsidered and withdrawn.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record.

Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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Date: **October 29, 2009**

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